UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AGAMATRIX, INC.

Petitioner

v.

DEXCOM, INC.

Patent Owner

U.S. PATENT NO. 9,750,460

TITLE: SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM

Case No. IPR2018- 01717

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,750,460

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EXHIBIT LIST

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1003	Expert Declaration of John L. Smith, Ph. D.
1004	Curriculum Vitae of John L. Smith, Ph. D.
1005	U.S. Patent No. 6,233,471 ("Berner")
1006	U.S. Patent No. 5,243,516 ("White")
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1016	Claim Construction Order in Inv. No. 337-TA-1075
1017	Dexcom's Petition for Review of Initial Determination in Inv. No. 337-TA-1075
1018	J.D. Newman, et al., "Catalytic Materials, Membranes, and Fabrication Technologies Suitable for the Construction of Amperometric Biosensors," *Anal. Chem.* 1995, *67,* 4594-4599.

1019	S.J. Updike, et al., "The Enzyme Electrode," *Nature*, June 3, 1967, 214, 986-988.
1020	*Not used*
1021	PCT International Publication No. WO 96/00110 ("Tamada")
1022	*Not used*
1023	*Not used*
1024	*Not used*
1025	U.S. Patent No. 6,284,126 ("Kurnik")
1026	Joseph Wang, "Glucose Biosensors: 40 Years of Advances and Challenges," *Electroanalysis*, vol. 13, no. 12, pp. 983-88 (2001).
1027	U.S. Patent No. 5,322,063 ("Allen").
1028	U.S. Patent No. 5,607,565 ("Azarnia").
1029	R. Sternberg et al., "Covalent Enzyme Coupling on Cellulose Acetate Membranes for Glucose Sensor Development," *Analytical Chemistry*, vol. 60, no. 24 (1988) ("Sternberg").
1030	U.S. Patent No. 4,757,022 ("Shults").
1031	Yu. B. Vassilyev et al., "Kinetics and Mechanism of Glucose Electrooxidation on Different Electrode-Catalysts, Part I. Adsorption And Oxidation On Platinum," *J. Electroanal. Chem.*, 196, pp. 105-125 (1985) ("Vassilyev")
1032	U.S. Patent Application Publication No. 2003/0094383 ("Kermani")
1033	U.S. Patent No. 6,433,602 ("Lall")
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1039	U.S. 6,890,421 ("Ohara-421")
1040	R. T. Kurnik, et al. "Design and Simulation of a Reverse lontophoretic Glucose Monitoring Device," *J. Electrochem. Soc.*, vol. 145, no. 12, pp. 4119-25 (1998) ("Kurnik-Article")

Citations in this petition to patents use the column and line number found within the document, rather than the page indicated by the exhibit label. Citations to the remaining exhibits refer to the page number of the underlying document. Emphasis is added, unless noted otherwise.

PETITION FOR *INTER PARTES* REVIEW

Pursuant to the provisions of 35 U.S.C. § 311 and 37 C.F.R. § 42.100 *et seq.*, Petitioner AgaMatrix, Inc. ("AgaMatrix," or "Petitioner") petitions the Patent Trial and Appeal Board to institute an *Inter Partes* Review ("IPR") of claims 14-69 ("challenged claims") of United States Patent No. 9,750,460 ("the '460 Patent," Ex. 1001) which is assigned to Dexcom, Inc. ("Dexcom" or "Patent Owner").

I. INTRODUCTION

The '460 Patent relates generally to systems and methods for processing data received from a glucose sensor. In particular, the challenged claims are directed to glucose sensor systems which employ sensor electronics to apply voltage(s) to an electrochemical glucose sensor, to measure a signal response of the sensor, and to evaluate the severity of an erroneous signal in order to decide whether to accept or discard a glucose measurement.

This was not a new idea before the priority date of the '460 Patent. In fact, multiple prior art references disclose similar electrochemical glucose sensors and related error-detection and error-rejection techniques. Ex. 1003, ¶¶12-14 and 88.

For example, U.S. Patent No. 6,233,471 ("Berner," Ex. 1005), discloses a signal processing method for continually or continuously measuring blood glucose concentration using a glucose sensor system such as a GlucoWatch™. Berner's biosensor includes an electrochemical cell and sensor electronics which apply and

switch voltages to the cell to measure raw glucose signals. Berner also teaches applying various data screens to invalidate or correct poor or incorrect signals based on predetermined criteria. Berner further teaches correcting the raw glucose signal by removing "baseline background" signal and reporting glucose concentrations.

U.S. Patent No. 5,497,772 ("Schulman," Ex. 1008) is directed to a glucose monitoring system that continuously measures blood glucose concentration. Schulman also discloses a display unit that displays not only the glucose concentration but also graphs and trends of glucose concentrations over user-selectable periods. Thus, Schulman discloses all the user interface limitations of the claimed sensor.

Since at least these prior art references disclose, teach or suggest all the elements of the challenged claims of the '460 Patent, as shown in this Petition, the cited references render all the challenged claims obvious. Ex. 1003, ¶¶88-89; *see id.*, ¶¶90-119.

II. TECHNOLOGY BACKGROUND

The technology at issue in the challenged claims relates to electrochemical sensors, specifically glucose sensors, and signal processing. Ex. 1003, ¶¶37-38.

A. Electrochemical Glucose Measurement

Glucose sensors typically come in two forms: Blood Glucose Meter (BGM) or Continuous Glucose Monitor (CGM), both of which were well known long before the priority date of the challenged claims. In general, BGMs provide episodic measurements of glucose outside the body while CGMs provide continuous monitoring of glucose inside the body. *Id.*, ¶¶39-40.

For each glucose measurement with a BGM device, a patient must prick his/her finger to extract a new blood sample and apply that sample to a single-use test strip inserted into the BGM device. An electrochemical reaction between the blood glucose and the chemicals on the test strip allows the BGM device to analyze the blood sample to determine the amount of glucose in the blood at the time the blood is extracted. *Id.*, ¶¶40-41.

CGMs, on the other hand, monitor glucose levels on a continuous basis and, as such, involve implanting some type of device into the patient's body or attaching a device thereto. Since the CGM sensor device is constantly exposed to a complex environment in or on the patient's body, CGMs typically pick up interferences (*i.e.*, noises) from the body and from other conditions in the body that are not picked up by BGMs. As a result, compared to BGMs, CGMs typically require more signal processing to correct for the extensive interferences they detect. *Id.*, ¶42.

Glucose levels are typically determined by measuring the concentration of an analyte in a chemical reaction based on electrochemistry. When a voltage is applied between two electrodes in a solution containing glucose (*e.g.*, a blood sample) and the required chemicals, electrochemical reactions at the electrodes may result in the consumption or release of electrons. These reactions cause the generation of electric current in an external circuit. It has long been discovered that, when a potential is applied to the electrodes in a solution containing an electroactive compound, such electric current is diffusion-limited and its decay over time generally follows the Cottrell relation in absence of significant errors. Such current can therefore indicate the analyte, e.g., glucose, concentration in the chemical reaction. *Id.*, ¶¶43-57.

This type of electrochemical glucose sensing method—applying a voltage across electrodes in an analyte solution to measure the resulting Cottrell current—and sensor devices implementing such a method—were well known in the art since at least the 1980s. *See*, *e.g.*, Ex. 1009, European Patent Application 0 230 472 ("Nankai") (disclosing amperometric techniques for determining glucose concentration); Ex. 1010, PCT International Publication No. WO 89/08713 ("Pottgen") (same). *Id.*, ¶58.

B. Error-Detection & Error-Rejection

Similarly, signal processing techniques, especially the concept of error-detection and error-rejection (*i.e.*, "keeping good data and rejecting bad data"), were generally known to those having ordinary skill in the art. *Id.*, ¶¶59-60. In particular, it was desirable and well known to detect signal errors and/or noises so as to reject measurements when the errors or noises are too severe. Indeed, various methods for screening and rejecting noisy or erroneous signals were well known, well understood, and applied in the glucose sensing art. *Id.*, ¶60.

For example, U.S. Patent No. 6,558,351 ("Steil," Ex. 1012), which is also in the field of glucose sensors, teaches evaluating measurement data against noise thresholds and discarding the data "if more than three values are outside of the noise thresholds." Steil, 23:24-33. Likewise, U.S. Patent No. 4,832,034 ("Pizziconi," Ex. 1013) teaches using a microprocessor in a glucose sensor to "discard artifacts" and "to automatically measure and compensate for temperature changes." Pizziconi, 23:58-65. *See also* U.S. Patent No. 6,309,884 ("Cooper," Ex. 1014), 9:3-50 (disclosing a number of error analysis methods which reject the entire glucose measurement session when the data meet certain criteria); U.S. Patent No. 6,153,069 ("Pottgen-069," Ex. 1015), 4:42-65 (disclosing the use of a calibration curve to identify abnormal amperometric glucose measurements that deviate from the expected Cottrell relationship). *Id.*, ¶61.

III. OVERVIEW OF THE '460 PATENT

A. Prosecution History

The '460 Patent issued from U.S. Patent Application No. 15/488,190, filed April 14, 2017, which is a continuation of U.S. Patent No. 9,649,069 ("the '069 Patent"). The '069 Patent, in turn, is a continuation patent in a line of continuations, tracing back to U.S. Patent Application No. 10/648,849, filed on Aug. 22, 2003 (now U.S. Patent No. 8,010,174).

On April 20, 2017, the applicant submitted two Information Disclosure Statements citing over 1,200 references.

On June 15, 2017, the applicant filed a preliminary amendment, canceling original claim 1-20, adding new claims 21-89, and making remarks on patent eligibility under Section 101. Ex. 1002, Prosecution History of U.S. Patent Application No. 15/481,347, pp. 220-52. The applicant also filed, and received approval of, an electronic terminal disclaimer with respect to U.S. Patent Application No. 15/481,347. Ex. 1002, pp. 212-19.

On July 6, 2017, a Notice of Allowance was issued and, on July 26, 2017, a Corrected Notice of Allowance was issued to correct some informalities in the claims. Ex. 1002, pp. 253-54 and pp. 385-88.

The '460 Patent issued on Sept. 5, 2017. Ex. 1001.

B. Summary of the Disclosure

The ’460 Patent is directed to systems and methods for processing data received from glucose sensors, specifically continuous glucose monitors. FIG. 1 illustrates such a glucose sensor 10:

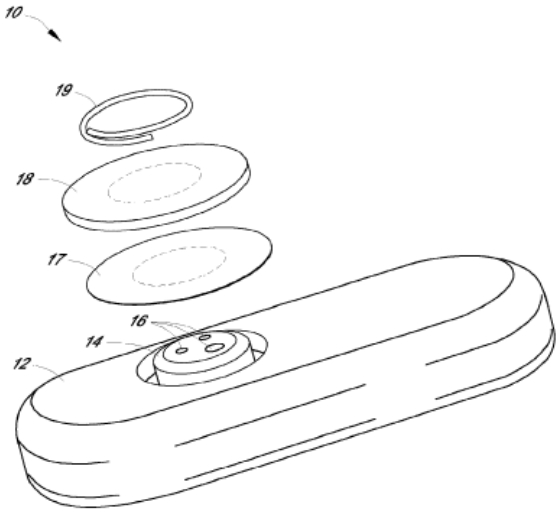

FIG. 1

Ex. 1001, FIG. 1.

The glucose sensor 10 includes three electrodes 16. *Id*. at 20:21-30. An enzyme, glucose oxidase, contained in the sensing membrane 17 “catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate[.]” *Id.* at 20:45-51. The amount of hydrogen peroxide (H_2O_2), which correlates to the amount of glucose in the sample, is measured to estimate glucose concentration which is consistent with the prior art electrochemical glucose sensing methods described above. *Id*. at 20:43-21:5.

The preferred embodiment disclosed in the ’460 Patent is a continuous

glucose monitor (CGM)—*i.e.*, a "system [that] monitors a data stream from a glucose sensor." *Id*, Abstract. *See also id.*, 16:1-6 (defining CGMs). Because CGMs are implanted in or maintain constant contact with the body, they capture interferences from the body, causing significant signal errors. The CGM of the '460 Patent purports to detect signal errors and make appropriate corrections. Figure 7A is a graph of a raw data stream, that includes a signal artifact/erroneous signal (as shown at region 74a), from a glucose sensor spanning about four hours:

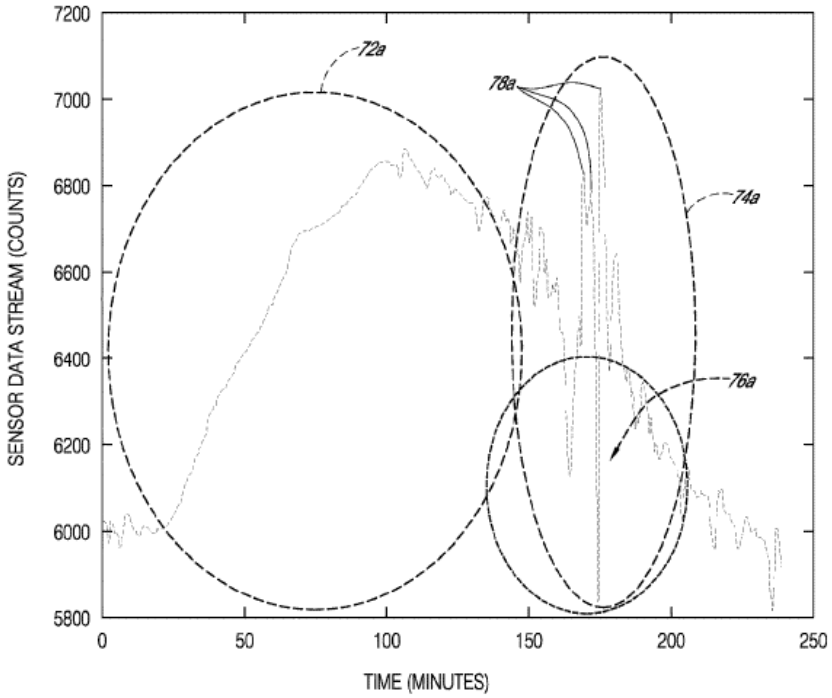

FIG. 7A

Ex. 1001, FIG. 7A.

The specification of the '460 Patent is limited to a virtually exclusive description of CGM embodiments, but the patent nevertheless states:

The glucose sensor can be any device capable of measuring

> ***the concentration of glucose.*** One exemplary embodiment is described below, which utilizes an implantable glucose sensor. However, it should be understood that ***the devices and methods described herein can be applied to any device capable of detecting a concentration of glucose and providing an output signal that represents the concentration of glucose***.

Ex. 1001, 20:13-20.

Thus, the inventors of the '460 Patent do not even say or suggest that they invented any new type of electrochemical sensor or a new sensing technique. Instead, they allege describing a robust error detection and correction technique. That technique, however, was also not novel or unobvious, as discussed below. Just as electrochemical glucose sensors had been known for decades before 2003, the sources introducing errors in the sensor signal, and techniques for detecting and correcting those errors, had also been well known for decades prior to 2003, as the references discussed below demonstrate.

C. Challenged Claims

The claims at issue in this Petition are claims 14-69, among which claims 14, 20, 26, 32, 38, 44, 50, 56, and 62-69 are independent claims.

Claim 14 reads:

[14.preamble] A glucose sensor system, the system comprising:
[14.a] an electrochemical glucose sensor configured to be in contact with a biological fluid to obtain a glucose measurement, wherein the electrochemical

glucose sensor comprises a first electrode, a second electrode, and an enzyme-containing film, wherein the first electrode comprises an electrode surface; and

[14.b] sensor electronics comprising a processor for executing computer program code stored in a memory to cause the processor to:

[14.c] apply a voltage to the electrochemical glucose sensor, wherein applying the voltage comprises at least one process selected from the group consisting of switching, cycling, and pulsing a voltage applied to the electrochemical glucose sensor;

[14.d] measure a signal response of the electrochemical glucose sensor responsive to the applying,

[14.e] detect an erroneous signal based at least in part on the signal response of the electrochemical glucose sensor to the applying,

[14.f] wherein the erroneous signal is associated with at least one condition selected from the group consisting of an ischemia, a pH, a temperature associated with the electrochemical glucose sensor, a biochemical species, an available electrode surface area, a local environment associated with the electrode surface of the first electrode, a diffusion transport of glucose or a measured species, and a pressure or a stress associated with the electrochemical glucose sensor,

[14.g] determine a value associated with a severity of the erroneous signal, and

[14.h] discard a glucose measurement when the value associated with the severity of the erroneous signal is outside of a predetermined threshold value.

Each of independent claims 20, 26, 32, 38, 50 and 56 includes substantially the same limitations as independent claim 14 except that: (1) the "wherein" clauses

in the "detect" step of those other independent claims each recites a single condition instead of a list of conditions as in claim element [14.f]; and (2) some of those other independent claims do not recite "wherein the first electrode comprises an electrode surface."

Independent claims 62-69 recite substantially the same limitations as independent claims 14, 20, 26, 32, 38, 44, 50, and 56 respectively, except that each of claims 62-69 adds a step of "generate a glucose value for display when the value associated with the severity of the erroneous signal satisfies a predetermined threshold value" and further includes more "user interface" functions.

The limitations of the independent claims may be sorted into hardware elements (i.e., electrochemical sensor and circuitry for its operation) and software elements (i.e., various signal analysis/processing and display operations).

As noted above, the universal applicability of the patent disclosure (as claimed in the specification) suggests that the combination of hardware elements is not novel or inventive. Indeed, those recited hardware elements are generic to any electrochemical glucose sensor device and were well known in the art.

Furthermore, the recited software elements (or functional steps) involve nothing more than basic operations of an electrochemical glucose sensor and the well-known signal processing concept of error-detection and error-rejection—that is, generating and displaying a glucose value only if a signal error is not too severe.

Thus, the claimed invention is really directed to a broad concept of "keeping good data and rejecting bad data" that is applied to conventional glucose sensors, i.e., an idea that is basic and fundamental to any signal processing system. As shown below, all these claimed hardware elements, their operations, and the recited signal processing operations were conventional, routine, and well-known prior to 2003.

IV. STATEMENT OF THE RELIEF REQUESTED

A. Claims for Which Review is Requested and the Statutory Grounds of Challenge

Petitioner respectfully requests that the Board institute an IPR of claims 14-69 of the '460 Patent and cancel those claims as unpatentable under pre-AIA 35 U.S.C. § 103, based on one or more of the following grounds:

Ground	***Statute***	***References***	***Claims***
1	§ 103	Berner	14-61
2	§ 103	Berner, Schulman	62-69

The grounds for unpatentability rely on the following references, which qualify as prior art under pre-AIA 35 U.S.C. § 102:

Exhibit.	***Prior art***	***Filing/Issued/Publication Date***	***Statute***
1005	U.S. Patent No. 6,233,471 ("Berner")	Filed May 11, 1999 Issued May 15, 2001	102(a)/(b)
1008	U.S. Patent No. 5,497,772 ("Schulman")	Filed Nov. 19, 1993 Issued Mar. 12, 1996	102(a)/(b)

Petitioner's arguments here were not considered by the Examiner, and Petitioner presents additional evidence not considered by the PTO, including the declaration of John L. Smith, Ph.D. (Ex. 1003). Dr. Smith has over 55 years of experience in electrochemical analytical instruments and systems, including 30 years in the glucose monitoring field. He worked at the LifeScan (diabetes care) division of Johnson & Johnson, as Vice President of Research, Development, and Engineering (and Chief Science Officer), for twelve years. Since his retirement from Johnson & Johnson, he has consulted for more than 40 blood glucose companies or their investors. From his extensive experience in the field, Dr. Smith has unparalleled knowledge of the glucose monitoring technology and its development history.

The Berner (Ex. 1005) and Schulman (Ex. 1008) patents were among the more than 1,200 references disclosed to the Patent Office (which include seven Berner patents and applications) in an Information Disclosure Statement, which contained no explanation regarding the references and provided the examiner with no guidance regarding which of the more than 1,200 cited reference were most pertinent to the claimed inventions. Ex. 1002 at 230-298, 305-337. The prosecution history confirms that neither patent was discussed by the examiner and there is no evidence in the prosecution history regarding how closely these two references out of the 1,200 cited references were analyzed by the examiner, if at

all. *See* Ex. 1002, pp. 207, 262, 212-54, and 385-88.

The rest of the identified prior art references were not before the Patent Office and therefore never considered during prosecution.

B. Level of Ordinary Skill

As explained by Dr. John L. Smith ("Dr. Smith"), who is an expert in this field, a person of ordinary skill in the art ("POSITA") at the time of the alleged invention would have had the equivalent of either (i) a bachelor's or master's degree in biology, chemistry, physics, electrical engineering, or related fields, and at least five years of experience developing glucose sensors or other biosensensors; or (ii) a Ph.D. with at least two years of experience in the same fields. Additional graduate education could substitute for professional experience, and significant work experience could substitute for formal education. Ex. 1003, ¶¶33-36.

V. CLAIM CONSTRUCTION

In an *inter partes* review, the claim terms should be given their plain meanings according to the broadest reasonable interpretation in light of the

specification.[1] *See Cuozzo Speed Technologies, LLC v. Lee*, 136 S.Ct. 2131 (2016).

In the related ITC proceeding (Investigation No. 337-TA-1075), the parties agreed on the interpretation of some claim terms, the judge construed some of the disputed terms, and Patent Owner offered "plain and ordinary meaning" interpretation of other disputed terms. Those terms, to the extent relevant to the challenged claims, are listed below with their definitions and indication of their sources. Petitioner believes that the broadest reasonable interpretation of the below-listed claim terms is *at least as broad as* the listed definitions.

Claim Term	Definition	Source[2]
electrochemical glucose sensor	a device by which glucose can be quantified in which chemical energy is converted to electrical energy	Parties
enzyme-containing film	a thin layer that includes an enzyme	Pat. Owner
apply a voltage to the electrochemical glucose	put to use a voltage to the	ITC judge

[1] Petitioner reserves the right to present different constructions in other forums (e.g., a district court, or the International Trade Commission) where a different claim construction standard applies.

[2] *See* Ex. 1016 at 14-15 ("Construction of the Agreed-Upon Claim Terms); *id*. at 24, 28, 30, 33, 35, 37, 40, 42 (judge-ordered definitions of disputed claim terms); Ex. 1017 (Dexcom's Petition for Review of ID) at 41-43, 50.

Claim Term	Definition	Source[2]
sensor	electrochemical glucose sensor	
switching, cycling, and pulsing a voltage	changing a voltage, periodically repeating a voltage, and abruptly changing a voltage for a brief interval	ITC judge
erroneous signal	signal that is not indicative of the glucose level	ITC judge
generate an estimated glucose concentration value when the severity associated with the signal artifact is evaluated to be under a predetermined threshold	to generate an estimated glucose concentration value for display to a user when the severity related to the signal artifact (as defined herein) is evaluated by the sensor electronics to be less than a predetermined threshold value	Parties
a voltage response of the electrochemical glucose sensor	voltage responsive to a condition of the electrochemical glucose sensor	ITC judge
available electrode surface area	surface area of an electrode where an electrochemical reaction occurs	Parties

VI. DETAILED GROUNDS FOR UNPATENTABILITY

A. Ground 1: Claims 14-61 are obvious under 35 U.S.C. § 103 in light of Berner.

U.S. Patent No. 6,233,471 to Berner et al. ("Berner," Ex. 1005) renders each of claims 14-61 obvious. Ex. 1003, ¶¶120-121.

1. Independent Claim 14

i. Berner discloses the preamble.

To the extent that the preamble is limiting, Berner discloses "[a] glucose sensor system." Ex. 1003, ¶¶122-125.

Berner discloses "methods for continually or continuously measuring the concentration of target chemical analytes present in a biological system" and notes in particular that "[o]ne important application of the invention involves ***a method for monitoring blood glucose concentrations***." Berner, 1:14-20; s*ee id*., Abstract. Berner also discloses a "***glucose monitoring device*** [that] is used to measure changes in glucose levels in an animal subject over a wide range of glucose concentrations." Berner, 13:42-47; Ex. 1003, ¶¶123-124.

Therefore, Berner discloses the preamble of claim 14. Ex. 1003, ¶125.

ii. Berner discloses "an electrochemical glucose sensor configured to be in contact with a biological fluid to obtain a glucose measurement, wherein the electrochemical glucose sensor comprises a first electrode, a second electrode, and an enzyme-containing film, wherein the first electrode comprises an electrode surface" (Element [14.a]).

<u>Part 1 of Element [14.a]:</u> "[A]n electrochemical glucose sensor configured to be in contact with a biological fluid to obtain a glucose measurement"

Berner describes "***a biosensor***[,] which comprises an ***electrochemical sensing element***," that is used for measuring "blood glucose." Berner, 2:59-61, 11:61-63, 14:13-25, and 34:24-27; *see id.*, 3:15-18 (describing ***glucose*** as the analyte of interest) and 13:34-41 (same).

Berner's biosensor is also "configured to be in contact with a biological fluid" because Berner describes "methods which extract samples from the

biological system by invasive, minimally invasive, and non-invasive sampling techniques, wherein ***the sensing apparatus is contacted with the extracted sample***," Berner, 2:43-67 and 11:41-53, and the extracted sample would be a biological fluid. Ex. 1003, ¶¶126-129.

Berner states that "[e]xamples of minimally invasive and noninvasive sampling techniques include ***iontophoresis***, . . . ***microfine (miniature) lances*** or cannulas[.]" Berner, 6:8-12. Regarding iontophoresis, Berner states that "[sampling] is carried out ***continually***," where "an iontophoretic current is applied to a surface of the skin of a subject," so that "ions or charged molecules pull along other uncharged molecules or particles such as glucose which are drawn into a collection reservoir placed on the surface of the skin." Berner, 13:51-57. Berner also states: "The term "reverse iontophoresis" refers to the movement of a substance from a ***biological fluid*** across a membrane by way of an applied electric potential or current. In reverse iontophoresis, a reservoir is provided at the tissue surface to receive the extracted material." Berner, 7:40-44. Additionally, Berner describes that "glucose is extracted into the hydrogel collection pad[.]" Berner, 14:18-24.

It was well known prior to 2003 that in non-invasive iontophoresis and reverse iontophoresis, "molecules or particles such as glucose" are typically extracted from the interstitial fluid, and are transported into the collection

reservoir/pad along with at least a fraction of the interstitial fluid or blood. *See* Ex. 1040, Kurnik-Article, p. 4119, col. 2, ¶ 1 ("Uncharged molecules (e.g., glucose) are carried along with the ions by convective transport. It is this ***convective flow that causes interstitial glucose to be transported across the skin***."); Ex. 1003, ¶¶130-132.

Berner also describes minimally-invasive techniques employing "***microfine (miniature) lances***" where samples may be extracted "across a membrane" that can be "***blood vessel tissue***[.]" Berner, 5:63-6:2. In this case, the samples would include blood. Ex. 1003, ¶133. Thus, the "extracted sample" that Berner describes includes the extracted molecules and a fraction of interstitial fluid or blood and, thus, constitutes a "biological fluid." *Id.*

Berner states explicitly that "***the sensing apparatus is contacted with the extracted sample***," Berner, 2:43-67 and 11:45-53. Specifically, collection reservoir/pad of the biosensor is in contact with the extracted sample, which is a biological fluid. Berner, 14:18-24; Ex, 1003, ¶134.

Therefore, Berner's biosensor is "configured to be in contact with a biological fluid," as claimed. Ex. 1003, ¶135.

<u>Part 2 of Element [14.a]:</u> "[W]herein the electrochemical glucose sensor comprises a first electrode, a second electrode, and an enzyme-containing film"

Berner's "'biosensor' or 'biosensor device' includes . . . a 'sensor element'

which includes . . . a '***biosensor electrode***' or '***sensing electrode***' or '***working electrode***'" and the "sensor element" can also include "***a 'reference electrode,' and a 'counter electrode.'***" Berner, 7:66-8:36; Ex. 1003, ¶136; *see also* Berner, 15:9-15 (describing ring-shaped iontophoretic electrodes 12, 14, and "a working electrode 16, a reference electrode 18, and a counter electrode 20"); FIGS. 1A, 1B; and 5:4-10; FIG. 4 (describing and depicting "bimodal electrodes 40 and 41; sensing electrodes 42 and 43; reference electrodes 44 and 45").

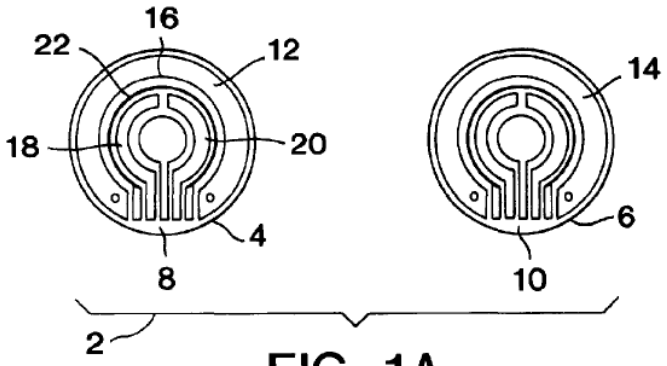

FIG. 1A

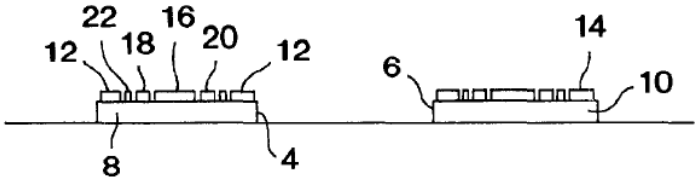

FIG. 1B

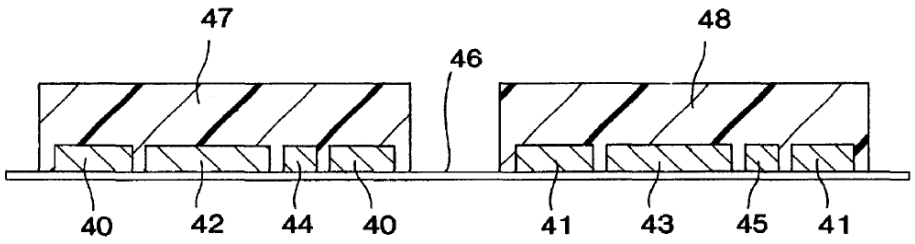

FIG. 4

Berner also teaches or suggests "an enzyme-containing film." First, Berner describes that "***an enzyme can be disposed in the collection reservoir***," and a "***suitable enzyme is glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide***." Berner, 10:58-11:11. Second, Berner teaches that the collection reservoirs (or "collection inserts") "can be ***in the form of a hydrogel*** (for example, ***in the shape of a disk or pad***)." Berner, 8:61-9:2. *See also id*., 6:26-35. Berner's hydrogel collection inserts contain glucose oxidase enzyme. *See* Berner, 14:18-24 (describing that "***glucose is extracted into the hydrogel collection pad where it contacts the GOx enzyme***."); *id.* 17:23-27 (describing "***a hydrogel collection reservoir system for monitoring glucose levels*** in a subject through the reaction of collected glucose ***with the enzyme glucose oxidase present in the hydrogel matrix***."). Ex. 1003, ¶¶137-143.

Berner's hydrogel "collection insert" is one of several *layers* in a "collection assembly":

> A 'collection assembly', as used herein, refers to ***structures comprised of several layers***, where the assembly includes at

> least one ***collection insert, for example a hydrogel***. An example of a collection assembly of the present invention is a mask layer, ***collection inserts***, and a retaining layer where the ***layers*** are held in appropriate, functional relationship to each other[.]

Berner, 9:34-43. Given the small dimensions of the collection reservoir(s) or collection insert(s), a POSITA would have known that the disk- or pad-shaped hydrogel containing the enzyme must be in the form of *a thin layer*. Ex. 1003, ¶¶144-145; *see* Berner, FIG. 1B (hydrogel pads 8, 10); FIG. 4 (hydrogel pads 47, 48).

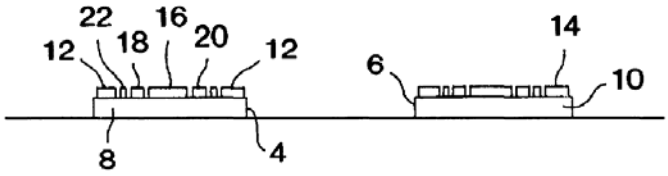

FIG. 1B

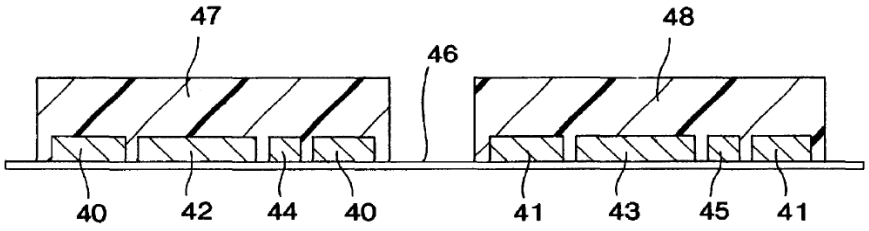

FIG. 4

Dr. Smith explains that a POSITA would have understood that, for a biosensor such as Berner's that continually measures glucose from the extracted samples, it would be desirable, if not critical, to provide the glucose enzyme

continually, e.g., in a film or membrane structure. Ex. 1003, ¶¶146-147. Indeed, Berner states that "the collection reservoir can be a receptacle containing a material which is ionically conductive (e.g., water with ions therein), or alternatively, it can be a material, such as, a sponge-like material or hydrophilic polymer, used to keep the water in place." Berner, 6:28-33. If the reservoir material keeps water in place, contained in a sponge-like material or hydrophilic polymer, it would also keep the much-larger enzyme molecules contained therein, i.e., in "*an enzyme containing film*." Ex. 1003, ¶147.

Berner also incorporates by reference[3] two articles which describe enzymes immobilized, i.e., contained, with thin layers of membranes. *See* Berner, 8:13-16 (citing Newman) and 7:58-65 (citing Updike). Newman (Ex. 1018) discloses an "enzyme electrode" having a thin layer of membrane containing glucose oxidase. Newman, p. 4595, col. 1, ¶4 – col. 2, ¶2; Ex. 1003, ¶148. Updike, Ex. 1019, discloses "immobilizing the enzyme glucose oxidase in a layer of acrylamide gel." Updike, p. 986, col. 2, ¶1; Ex. 1003, ¶149. Therefore, Berner teaches, or at least suggests, that its enzyme-containing hydrogel pads are *enzyme-containing films*, as claimed. Ex, 1003, ¶150.

[3] Berner explicitly incorporates by reference "[a]ll publications, patents and patent applications cited herein." Berner, 5:32-34.

<u>Part 3 of Element [14.a]:</u> "[W]herein the first electrode comprises an electrode surface"

Berner discloses this feature because Berner states: "The sensing electrode comprises ***a reactive surface*** which converts the analyte, or a derivative thereof, to electrical signal[.]" Berner, 8:6-8. Moreover, working, reference, and counter electrodes 16, 18, and 20, respectively, are shown in FIG. 1B as having top flat surfaces, and working electrodes 42 and 43 and reference electrodes 44 and 45 are shown in FIG. 4 as having top flat surfaces.

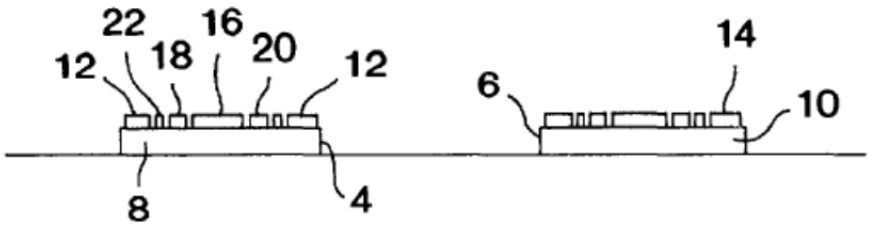

FIG. 1B

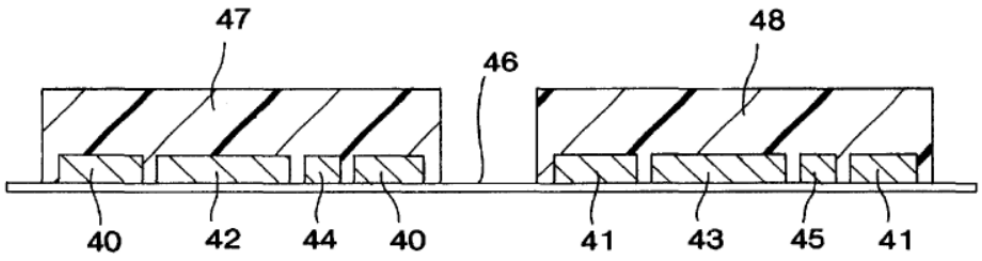

FIG. 4

Therefore, Berner discloses Element [14.a]. Ex. 1003, ¶¶151-152.

iii. Berner discloses "sensor electronics comprising a processor for executing computer program code stored in a

memory to cause the processor to [perform certain recited functions]" (Element [14.b]).

Berner's biosensing system includes a "sampling device," Berner, 13:25-34, where a "'housing' for the sampling system can further include ***suitable electronics*** (e.g., ***microprocessor***, memory, display and other circuit components) and power sources for operating the sampling system[.]" Berner, 6:40-43,; Ex. 1003, ¶¶153-155. Berner further states that the "[o]peration of the ***iontophoretic sampling device 30 is controlled by*** a controller 36 ***(e.g., a microprocessor)***[.]" Berner, 16:39-50.

Berner also describes that the controller/microprocessor executes a stored computer program to perform various operations:

> The ***microprocessor generally uses a series of program sequences to control the operations of the sampling device, which program sequences can be stored in the microprocessor's read only memory (ROM).*** Embedded software (firmware) controls activation of measurement and display operations, . . . setting and display of high and low analyte value alarms, . . . and display of stored readings. Sensor signals obtained from the sensor electrodes are processed before storage and display by one or more signal processing functions or algorithms[.]

Berner, 19:15-26.

Therefore, Berner discloses Element [14.b]. Ex. 1003, ¶¶156-158.

iv. Berner discloses "apply a voltage to the electrochemical glucose sensor, wherein applying the voltage comprises at least one process selected from the group consisting of switching, cycling, and pulsing a voltage applied to the electrochemical glucose sensor" (Element [14.c]).

Berner teaches this element because Berner describes applying voltages to different sets of electrodes of the biosensor. Berner also describes alternating the polarities of the voltage applied to one pair of electrodes, i.e., *cycling* the applied voltage, and applying voltages to different pairs of electrodes at different times, i.e., *switching* the applied voltage. Ex. 1003, ¶¶159-160. Specifically, Berner describes:

> ***In use, an electric potential*** . . . ***is applied between the two iontophoretic electrodes 12 and 14*** such that current flows from the first iontophoretic electrode 12 . . . into the skin or mucosal surface, and then . . . to the second iontophoretic electrode 14. The current flow is sufficient to extract substances including an analyte of interest through the skin into one or both of collection reservoirs 4 and 6. * * * In a preferred embodiment, the device is used for continual or continuous monitoring, and ***the polarity of iontophoretic electrodes 12 and 14 is alternated at a rate of about one switch every 10 seconds to about one switch every hour so that each electrode is alternately a cathode or an anode***.

Berner, 16:7-26; FIG. 2. Berner further states:

> The general operation of an iontophoretic sampling system is the ***cyclical repetition of two phases***: (1) a reverse-iontophoretic phase,

> followed by a (2) sensing phase. ***During the reverse iontophoretic phase, the first bimodal electrode*** (FIGS. 4, 40) ***acts as an iontophoretic cathode and the second bimodal electrode*** (FIGS. 4, 41) ***acts as an iontophoretic anode*** to complete the circuit. * * * ***During the sensing phase***, in the case of glucose, ***a potential is applied between the reference electrode*** (FIGS. 4, 44) ***and the sensing electrode*** (FIGS. 4, 42). The chemical signal reacts catalytically on the catalytic face of the first sensing electrode (FIGS. 4, 42) producing an electrical current, while the ***first bi-modal electrode (FIGS. 4, 40) acts as a counter electrode to complete the electrical circuit***.

Berner, 17:6-22; FIG. 4.

Thus, Berner describes applying a voltage across the first and second bi-modal electrodes during the reverse-iontophoretic phase, and then switching the applied voltage during the sensing phase by applying a voltage between the reference and sensing electrodes. Ex. 1003, ¶¶161-163.

Therefore, Berner discloses Element [14.c]. *Id.*

v. Berner discloses "measure a signal response of the electrochemical glucose sensor responsive to the applying" (Element [14.d]).

Berner discloses this element because Berner describes measuring a "raw amperometric signal" or current from working/sensing electrode of the biosensor during the sensing phase. Ex. 1003, ¶¶164-165. For example, Berner states:

"***Power and reference voltage are provided to the sensor electrode***s, and signal amplifiers can be used to ***process the signal from the working electrode or electrodes***." Berner, 16:46-49. Berner also states that the "iontophoretic sampling device is used to extract the analyte from the biological system, and ***a raw amperometric signal (e.g., nanoampere (nA) signal) is generated from the associated electrochemical biosensor device.***" Berner, 21:60-22:2.

Additionally, Burner states that "the ***surface of the sensing electrode that*** . . ., when composed of a reactive material, is sufficient to drive the electrochemical reaction at a rate sufficient to ***generate a detectable, reproducibly measurable, electrical signal*** that is correlatable with the amount of analyte present in the electrolyte." Berner, 8:44-60; Ex. 1003, ¶¶166-168.

Berner also states: "During the sensing phase, in the case of glucose, a potential is applied between the reference electrode (FIGS. 4, 44) and the sensing electrode (FIGS. 4, 42). The chemical signal reacts catalytically on the catalytic face of the first sensing electrode (FIGS. 4, 42) ***producing an electrical current***" which, as described above, is sensed and measured as the "raw amperometric signal" used for determining the amount of the analyte. Berner, 17:15-22; *see id.*, 18:18-21 ("For the purpose of the present sampling system, ***the electrical current measured at the sensing electrode subassembly*** is the current that is correlated with an amount of chemical signal."); Ex. 1003, ¶169.

Thus, Berner discloses Element [14.d] as claimed. *Id.*, ¶170.

vi. Berner discloses "detect an erroneous signal based at least in part on the signal response of the electrochemical glucose sensor to the applying" (Element [14.e]).

Berner teaches this claim element because Berner describes at least two kinds of "*erroneous signals*" and detection thereof, as discussed below.

Case 1:

Berner describes that the raw amperometric signal response may include "poor or incorrect signals," which can be detected and eliminated in a "data screening step." Ex. 1003, ¶¶171-173.

Specifically, Berner states that the "iontophoretic sampling device is used to extract the analyte from the biological system, and ***a raw amperometric signal (e.g., nanoampere (nA) signal) is generated*** from the associated electrochemical biosensor device. ***This raw signal can optionally be subjected to a data screening step (Step B) to eliminate poor or incorrect signals***, or can be entered directly into a conversion step to obtain an initial signal output which is indicative of the amount of analyte extracted by the sampling system." Berner, 21:60-22:2.

Berner also states:

> The raw signal obtained from the above-described glucose monitoring device can be screened to ***detect deviations from expected behavior which are indicative of poor or incorrect signals that will not correlate with blood glucose***.

Berner, 19:33-36.

> [T]he electrochemical signal during each sensing cycle is expected to behave as a smooth, monotonically decreasing signal which represents depletion of the hydrogen peroxide by the sensor electrode. ***Significant departure from this expected behavior is indicative of a poor or incorrect measurement*** (e.g., a non-monotonically decreasing signal is ***indicative of excessive noise*** in the biosensor signal), and thus ***monitoring signal behavior during sensing operations provides yet a further data screen for invalidating or correcting measurements***.

Berner, 20:47-56; *see id.*, 21:10-11 ("A ***large change in the peak of a sensor reading*** indicates a noisy signal.").

As such, the uncorrected raw amperometric signal can constitute an erroneous signal,[4] and screening of the raw amperometric signal constitutes detection thereof, as this claim element requires. Ex. 1003, ¶¶174-178.

Case 2:

Berner also describes that a "background signal" indicating a "baseline background interference" can be detected from the raw amperometric signal and,

[4] Erroneous signal may be construed at least as broadly as "a signal that is not indicative of the glucose level," *see* § V, above, and the uncorrected raw amperometric signal may not indicate the glucose level.

as such, detection of the background signal constitutes *detecting an erroneous signal based at least in part on the signal response.* Ex. 1003, ¶179.

In particular, Berner describes unadjusted background signals, i.e., *erroneous signals*, as follows:

> [T]he "baseline background," which, in the context of electrochemical detection, is a current (nA) generated by the sensing device independent of the presence or absence of the analyte of interest. This ***baseline background interferes with measurement of analyte of interest, and the amount of baseline background can vary with time, temperature and other variable factors.***
>
> * * *
>
> [I]n one embodiment of the invention, a baseline background subtraction method is used during the conversion step in order to reduce or eliminate such background interferences from the measured initial signal output. * * * ***After the device has been activated for a suitable period of time, and a stable signal is obtained, a measurement is taken from the sensor which measurement can then be used to establish a baseline background signal value.*** This background signal value is subtracted from an actual signal measurement value (which includes both analyte-specific and background components) to obtain a corrected measurement value. This baseline background subtraction method can be expressed using the following function:
>
> $i(\tau)=i_{raw}(\tau)-i_{bkgnd}(\tau)$

wherein: **($i_{raw}(\tau)$)** ***is the current measured by the sensor*** (in nA) at time τ; (τ) is the time after activation of the sensor; **($i_{bkgnd}(\tau)$)** ***is the background current*** (in nA); and **(i(τ))** ***is the corrected current*** (in nA). ***Measurement of the baseline background signal value is taken close in time to the actual signal measurement***[.]

Berner, 22:11-53.

Berner also describes the detection of a temperature adjusted baseline background (i.e., *erroneous*) signal:

> [T]ransient ***changes in temperature*** during or between measurement cycles, or between measurements of blank and active signals, ***can alter background signal***, reaction constants and/or diffusion coefficients.

Berner, 19:62-66.

> Plotting the natural log of the background current versus the reciprocal of temperature provides a linear function having a slope of (−K**1**). Using a known or derived value of K**1** allows the baseline current at any time (τ) to be corrected using the following function (which is referred to herein as the "K1 temperature correction"):
>
> $$i_{bkgnd,corrected} = i_{bkgnd,\tau_0} \exp[-K1(\frac{1}{T_\tau} - \frac{1}{T_{\tau_0}})]$$
>
> wherein: **($i_{bkgnd,corrected}$)** ***is the temperature corrected baseline current***[.]

Berner, 23:33-48.

Thus, according to Case 1, Berner describes "monitoring signal behavior" to detect "significant departure from [] expected behavior" that is indicative of "incorrect measurement" and, according to Case 2, the detection of background current, which represents measurement errors due to interferences, and determination of temperature-dependent background current, and thus discloses Element [14.e]. Ex. 1003, ¶¶180-183.

vii. Berner discloses "wherein the erroneous signal is associated with at least one condition selected from the group consisting of an ischemia, a pH, a temperature associated with the electrochemical glucose sensor, a biochemical species, an available electrode surface area, a local environment associated with the electrode surface of the first electrode, a diffusion transport of glucose or a measured species, and a pressure or a stress associated with the electrochemical glucose sensor" (Element [14.f]).

Berner explicitly states that "($i_{bkgnd,corrected}$) is the ***temperature corrected*** baseline current," i.e., an ***erroneous signal that is associated with a temperature***." *See* Berner, 23:33-48; Ex. 1003, ¶¶184-185. Additionally, the background signal may be associated with diffusion transport of hydrogen peroxide (i.e., *a measured species*). Berner also states that the "GOx enzyme converts glucose and oxygen in the hydrogel to hydrogen peroxide which diffuses to the sensor and is catalyzed by the sensor to" "generate an electrical signal," Berner 14:20-24, and that "transient changes in temperature . . . can alter background signal, reaction constants and/or diffusion coefficients." Berner 19:62-66. The background signal may also be

associated with other conditions, as described below in the discussion of claims 20, 26, 32, 38, 44, 50, and 56. Ex. 1003, ¶¶186-187.

Therefore, Berner discloses Element [14.f]. Ex. 1003, ¶188.

viii. Berner discloses "determine a value associated with a severity of the erroneous signal" (Element [14.g]).

Berner discloses at least two ways in which a value associated with the severity of an erroneous signal that is part of the measured signal is determined. Ex. 1003, ¶¶189-190.

Case 1:

Berner describes that a value of the baseline background current signal (which may represent and quantify the baseline background interferences) is determined. This value may be subtracted from the raw amperometric signal value, to obtain a current value that is used to determine the glucose concentration. Ex. 1003, ¶191. Specifically, Berner states:

> ***After the device has been activated for a suitable period of time, and a stable signal is obtained, a measurement is taken from the sensor which measurement can then be used to establish a baseline background signal value.*** This background signal value is subtracted from an actual signal measurement value (which includes both analyte-specific and background components) to obtain a corrected measurement value. This baseline background subtraction method can be expressed using the following function:

$i(\tau)=i_{\text{raw}}(\tau)-i_{\text{bkgnd}}(\tau)$

wherein: (**$i_{raw}(\tau)$**) ***is the current measured by the sensor*** (in nA) at time τ; (τ) is the time after activation of the sensor; (**$i_{bkgnd}(\tau)$**) ***is the background current*** (in nA); and (**$i(\tau)$**) ***is the corrected current*** (in nA). ***Measurement of the baseline background signal value is taken close in time to the actual signal measurement***[.]

Berner, 22:31-53.

In addition, the baseline background current signal may be adjusted for temperature. To this end Berner states:

> Plotting the natural log of the background current versus the reciprocal of temperature provides a linear function having a slope of (−K**1**). Using a known or derived value of K**1** allows the baseline current at any time (τ) to be corrected using the following function (which is referred to herein as the "K1 temperature correction"):
>
> $$i_{bkgnd,corrected} = i_{bkgnd,\tau_0} \exp[-K1(\frac{1}{T_\tau} - \frac{1}{T_{\tau_0}})]$$
>
> wherein: ($i_{bkgnd,corrected}$) is the temperature corrected baseline current[.]

Berner, 23:33-48. Because "the background signal value is subtracted from an actual signal measurement value . . . to obtain a corrected measurement value," see Berner, 22:11-53, the unadjusted and temperature-adjusted background current

values are *values associated with the severity of an erroneous signal*. Ex. 1003, ¶¶192-193.

Furthermore, Berner describes that a difference between two values of background current also indicate the level of noise and, as such, the difference value is also a value associated with the severity of the erroneous signal. *Id.*, ¶194. In particular, Berner states:

> ***Background Stability [] check is to determine if the background current is changing too excessively, which indicates a noisy signal*** and can result in inaccurate glucose readings. If the ***percentage difference between successive background measurements is greater than or equal to a predetermined value***, for example, 15%, then an error is indicated.

Berner, 21:30-36.

Case 2:

Berner also describes computing the difference between the successive peaks of the measured current signal, where the difference indicates the severity of the noise in the measured signal, i.e., the severity of the erroneous signal component of the measured signal. Ex. 1003, ¶195. In particular, Berner states:

> signal—Peak Stability. ***A large change in the peak of a sensor reading indicates a noisy signal.*** The peak of any given cathodal half cycle is defined as the difference between the first biosensor point and the temperature corrected average of the last two points from the

previous anodal half cycle. If the ***percentage difference between successive peaks*** from the same sensor is greater than a predetermined value, for example, 30%, then an error is indicated.

Berner, 21:10-18.

Therefore, according to Cases 1 and 2, Berner discloses Element [14.g]. Ex. 1003, ¶196.

ix. Berner discloses "discard a glucose measurement when the value associated with the severity of the erroneous signal is outside of a predetermined threshold value" (Element [14.h]).

Berner discloses this claim element because Berner describes discarding a measured signal if in a data screen the severity of signal error is determined to exceed a predetermined threshold. Ex. 1003, ¶¶197-198. In particular, Berner describes ***comparing the two types of error severity values***, i.e., value of the baseline background current (as described in Case 1, above) and peak-to-peak variation in the measured signal (as described in Case 2, above) ***with respective thresholds*** to determine whether error must be reported and/or the glucose measurement must be discarded as opposed to computing glucose concentration. *Id.*

Case 1:

In the discussion of claim element [14.g], Case 1 identifies a difference between two values of the baseline background current (which may be unadjusted

or temperature-adjusted) as a value associated with the severity of the erroneous signal. Ex. 1003, ¶199; *see* Berner, 22:11-53 and 23:33-48. Berner further discloses discarding a measurement when this background difference value exceeds a corresponding threshold:

> Background Stability [] check is to determine if the background current is changing too excessively, which indicates a noisy signal and can result in inaccurate glucose readings. ***If the percentage difference between successive background measurements is greater than or equal to a predetermined value***, for example, 15%, then an error is indicated.

Berner, 21:30-36; Ex. 1003, ¶199.

Case 2:

Additionally, in the discussion of claim element [14.g], Case 2 identifies a difference between two peaks of the measured signal as another value associated with the severity of the erroneous signal. Berner discloses discarding a measurement when this peak-to-peak difference exceeds a corresponding threshold:

> The raw signal obtained from the above-described glucose monitoring device can be screened to detect deviations from expected behavior which are indicative of poor or incorrect signals that will not correlate with blood glucose. ***Signals that are identified as poor or incorrect in this data screen may be discarded*** or otherwise corrected for prior to

> any signal processing and/or conversion in order to maintain data integrity.

Berner, 19:33-40; Ex. 1003, ¶200. Berner also states:

> signal—Peak Stability. ***A large change in the peak of a sensor reading indicates a noisy signal.*** The peak of any given cathodal half cycle is defined as the difference between the first biosensor point and the temperature corrected average of the last two points from the previous anodal half cycle. If the ***percentage difference between successive peaks*** from the same sensor is greater than a predetermined value, for example, 30%, then an error is indicated.

Berner, 21:10-18.

Therefore, according to Cases 1 and 2, Berner discloses Element [14.g] as claimed. Ex. 1003, ¶¶201-202.

Thus, Berner teaches or at least suggests each and every element of claim 14 and, thus, renders claim 14 unpatentable as being obvious. *Id.*, ¶203.

2. Independent Claim 20

This claim is substantially the same as independent claim 14 except for the claim element [14.f], which is replaced with the claim element "wherein the erroneous signal is associated with an available electrode surface area."

Berner discloses or at least suggests this claim element because Berner describes biosensors employing continuous transdermal iontophoretic extraction of glucose, *see* Berner, 13:51-61, and prior to the alleged invention of the '460 Patent,

the deterioration of the electrode surface area available for an electrochemical reaction was a known, commonly occurring problem in such biosensors. Ex. 1003, ¶¶204-205.

Specifically, Berner describes:

> Sampling is carried out ***continually*** by non-invasively extracting glucose through the skin of the patient. More particularly, an ***iontophoretic current is applied*** to a surface of the skin of a subject. When the current is applied, ions or charged molecules ***pull along*** other ***uncharged molecules or particles such as glucose which are drawn into a collection reservoir*** placed on the surface of the skin.

Berner, 13:51-61.

It was well known prior to the alleged invention of the '460 Patent that these molecules and any products of the electrochemical reaction can accumulate on the electrode surface during the continuous use of the sensor, typically causing the electrode surface area available for electrochemical reaction to decrease over time, introducing measurement errors. Ex. 1003, ¶¶206-207.

For example, Kurnik U.S. Patent No. 6,284,126 (Ex. 1025) describes a biosensor for glucose measurement that is similar to Berner's. *Id.*, ¶208. In particular, like Berner's glucose sensor, Kurnik's glucose sensor also uses a hydrogel containing glucose oxidase for the enzymatic reaction and "iontophoresis or reverse iontophoresis" "to draw glucose into the hydrogel." Kurnik, 3:6-21 and

13:9-20; FIG. 4. Kurnik states:

> [T]he hydrogel patches and the electrodes of the present invention used with the electrode assembly are generally designed so as to provide utility over a period of about 24 hours. ***After that time some deterioration in characteristics, sensitivity, and accuracy of the measurements from the electrode can be expected*** (e.g., ***due to accumulation of material on the face of the electrode subassembly***)[.]"

Kurnik, 13:22-32.

The adsorption of materials on the surface of platinum electrodes, the type of electrode that Berner describes, Berner 4:59-61, 8:8-10, 14:59-15:2, and 35:15-17, was well known by a POSITA to be a limitation of that material when it is re-used for multiple measurements without intervening chemical or electrochemical cleaning. *See, e.g.*, Vassilyev (Ex. 1031), p. 112, ¶4 ("Our preliminary data on the adsorption of gluconic acid, [] show that it is adsorbed on the platinum electrode[.]"); Ex. 1003, ¶¶209-210.

Therefore, as Dr. Smith explained, a POSITA would have readily understood and appreciated that the raw amperometric current signal (i.e., an erroneous signal according to Case 1 discussed in claim element [14.e]), and the unadjusted and temperature adjusted baseline current signals (i.e., erroneous signals according to Case 1 discussed in claim element [14.e]) may all be *associated with an available electrode surface area*, because that area may change

over time during continuous glucose monitoring due to the accumulation of extracted materials and those produced in the electrochemical reaction. Id.

Moreover, as discussed above in connection with claim 14, Berner teaches or at least suggests all of the other elements of claim 20. As such, Berner renders claim 20 obvious. *Id.*, ¶211.

3. Independent Claim 26

This claim is substantially the same as independent claim 14 except for the claim element [14.f], which is replaced with the claim element "wherein the erroneous signal is caused by a temperature associated with the electrochemical glucose sensor."

Berner teaches this element because Berner describes correcting the raw amperometric signal (i.e., the measured response) according to a baseline signal (i.e., *the erroneous signal*) that is temperature dependent. Ex. 1003, ¶¶212-213.

Berner states:

> [T]ransient ***changes in temperature*** during or between measurement cycles, or between measurements of blank and active signals, ***can alter background signal***, reaction constants and/or diffusion coefficients.

Berner, 19:62-66. Berner further states:

> Plotting the natural log of the background current versus the reciprocal of temperature provides a linear function having a slope of

(−K**1**). Using a known or derived value of K**1** allows the baseline current at any time (τ) to be corrected using the following function (which is referred to herein as the "K1 temperature correction"):

$$i_{bkgnd,corrected} = i_{bkgnd,\tau_0} \exp[-K1(\frac{1}{T_\tau} - \frac{1}{T_{\tau_0}})]$$

wherein: ($\boldsymbol{i_{bkgnd,corrected}}$) ***is the temperature corrected baseline current***[.]

Berner, 23:33-48. Thus, ($i_{bkgnd,corrected}$) constitutes an *erroneous signal caused by a temperature associated with the electrochemical glucose sensor.* Ex. 1003, ¶213.

Moreover, as discussed above in connection with claim 14, Berner teaches or at least suggests all of the other elements of claim 26. As such, Berner renders claim 26 obvious. *Id.*, ¶214.

4. Independent Claim 32

This claim is substantially the same as independent claim 14 except for the claim element [14.f], which is replaced with the claim element "wherein the erroneous signal is associated with a local environment associated with the electrode surface of the first electrode."

As discussed above in connection with claim 20, the ***surfaces of electrodes*** in a glucose sensor such as the one that Berner describes ***can be affected by the accumulation of materials*** extracted from the tissue and/or produced during the

electrochemical reaction, which can cause an error in the glucose measurement. *See* Berner, 13:51-61; Kurnik, 13:22-32; Ex. 1003, ¶¶215-216. An erroneous signal corresponding to the accumulation of materials on the electrode surface is also an erroneous signal *associated with a local environment associated with the electrode surface of at least one electrode*. Ex. 1003, ¶216.

Moreover, Berner describes that uncharged molecules or particles from the subcutaneous tissue (including glucose) are pulled into a collection reservoir of the biosensor. *See* Berner, 13:51-61. Dr. Smith explained that the electric potential difference that is necessary to pull glucose molecules would also pull other molecules such as protein molecules, bilirubin, etc. Ex. 1003, ¶217. According to Berner, these other non-glucose molecules, that may include "electrochemically active interfering species," would be present in the collection reservoir, i.e., in the local environment associated with the electrode surface of at least one electrode. *See* Berner, 13:54-61 and 22:18-21; Ex. 1003, ¶218. Berner also states that the "electrochemically active interfering species . . . present in the device" can "interfere with measurement of the analyte of interest," causing a measurement error. Berner, 22:18-21. As such, Berner's erroneous signals may be *associated with a local environment associated with the electrode surface of at least one electrode* for this additional reason. Ex. 1003, ¶219.

As discussed above in connection with claim 14, Berner teaches or at least

suggests all of the other elements of claim 32. As such, Berner renders claim 32 obvious. *Id.*, ¶220.

5. Independent Claim 38

This claim is substantially the same as independent claim 14 except for the claim element [14.f], which is replaced with the claim element "wherein the erroneous signal is associated with a diffusion transport of glucose or a measured species."

Berner discloses or at least suggests this claim element because Berner describes that the temperature related measurement error can also be related to the diffusion transport of hydrogen peroxide, which is a measured species. Ex. 1003, ¶¶221-222. In particular, Berner states:

> The ***GOx enzyme converts glucose*** and oxygen in the hydrogel ***to hydrogen peroxide which diffuses to the sensor*** and is ***catalyzed by the sensor to*** regenerate oxygen and ***form electrons. The electrons generate an electrical signal that can be measured***, analyzed, and correlated to blood glucose.

Berner, 14:14-25. Thus, hydrogen peroxide in Berner's biosensor is a measured species. Ex. 1003, ¶222.

Berner also states:

> As with any chemical sensing method, ***transient changes in temperature*** during or between measurement cycles, or between

measurements of blank and active signals, ***can alter background signal***, reaction constants ***and/or diffusion coefficients***.

Berner, 19:62-66. In discussing claim element [14.e], it is explained that the temperature-based background signal is an erroneous signal and, hence, that erroneous signal may also be associated with the *diffusion transport of* hydrogen peroxide, i.e., *a measured species*. Ex. 1003, ¶¶223-224.

As discussed above in connection with claim 14, Berner teaches or at least suggests all of the other elements of claim 38. As such, Berner renders claim 38 obvious. *Id.*, ¶225.

6. Independent Claim 44

This claim is substantially the same as independent claim 14 except for the claim element [14.f], which is replaced with the claim element "wherein the erroneous signal is associated with a pressure or a stress associated with the electrochemical glucose sensor."

As part of screening, i.e., detecting various error conditions, Berner describes detecting errors due to mechanical disturbance that may be caused by pressure or stress. *See* Berner, 21:3-9 (describing screening, in general); 21:37-44 (describing a voltage screen); Ex. 1003, ¶¶226-227. Berner states:

> ***If the glucose monitoring device is mechanically disturbed, there can be a larger change*** (e.g., larger relative to when the monitor is functioning under normal conditions) ***in iontophoresis voltage***. This

> could ***lead to an aberrant reading***. If the percentage difference between successive cathodal or anodal iontophoresis voltages is gr[e]ater than a predetermined value, for example, 15%, then an error is indicated.

Berner, 21:37-44.

A POSITA would have understood that Berner's glucose monitoring device would be "mechanically disturbed" if subjected to pressure and/or stress, for example, when the wearer is jogging or riding in a car on an unpaved road. Ex. 1003, ¶228. Because this condition can "lead to an aberrant reading," the background or baseline signals that Berner describes (i.e., *the erroneous signals*) may represent an error caused by the mechanical disturbance, which would have been caused by the pressure and/or stress experienced by the glucose monitor. *Id.*, ¶229. As such, Berner discloses that "*the erroneous signal is associated with a pressure or a stress associated with the electrochemical glucose sensor.*" *Id.*

As discussed above in connection with claim 14, Berner teaches or at least suggests all of the other elements of claim 44. As such, Berner renders claim 44 obvious. *Id.*, ¶230.

7. Independent Claim 50

This claim is substantially the same as independent claim 14 except for the claim element [14.f], which is replaced with the claim element "wherein the erroneous signal is associated with a biochemical species."

Berner states "electrochemically active interfering species and/or residual analyte can be present in the device which will further interfere with measurement of the analyte of interest." Berner 22:18-21. Thus, Berner indicates that, in addition to erroneous signals from other electrochemically active biochemical species (such as bilirubin or acetaminophen) extracted from skin by reverse iontophoresis, erroneous signals can result from any analyte (glucose) and gluconate, which are also a biochemical species, that remain in the reservoir from a previous extraction/reaction. Ex. 1003, ¶¶231-232.

Also, as discussed above in connection with claim 20, the ***surfaces of electrodes*** in a glucose sensor such as the one that Berner describes ***can be affected by the accumulation of materials*** extracted from the tissue and/or produced during the electrochemical reaction, which can cause an error in the glucose measurement. *See* Berner, 13:51-61; Kurnik, 13:22-32; Ex. 1003, ¶232. Moreover, Berner describes that uncharged molecules or particles from the subcutaneous tissue (including glucose) are pulled into a collection reservoir of the biosensor. *See* Berner, 13:51-61. Dr. Smith explained that the electric potential difference that is necessary to pull glucose molecules would also pull other molecules such as protein molecules, bilirubin, etc., which are biochemical species. Ex. 1003, ¶233. As such, an erroneous signal corresponding to the accumulation of materials on the electrode surface and/or to the interference from the materials

(including biochemical species) pulled into the collection reservoir of the glucose sensor can be an erroneous signal *associated with a biochemical species*. *Id.*

As discussed above in connection with claim 14, Berner teaches or at least suggests all of the other elements of claim 50. As such, Berner renders claim 50 obvious. *Id.*, ¶234.

8. Independent Claim 56

This claim is substantially the same as independent claim 14 except for the claim element [14.f], which is replaced with the claim element "wherein the erroneous signal is associated with an oxygen deficit."

Berner teaches or at least suggests this claim element because Berner describes or at least suggests sensors using blood samples for glucose measurement, where glucose in the extracted blood sample would react with oxygen and be converted into hydrogen peroxide for measurement thereof, Berner, 13:62-68, and a POSITA would have known that in such sensors, oxygen deficit is a well-known source of error. Ex. 1003, ¶¶235-236.

Specifically, Berner describes minimally invasive and non-invasive sampling techniques that may use, e.g., "***microfine (miniature) lances or cannulas***," and the "biological system" from which the sample is extracted may include "***blood vessel tissue***." Berner, 5:60-6:12; Ex. 1003, ¶237.

A POSITA would have understood that sampling performed using

"microfine (miniature) lances," or "micro-needles" (which Berner describes can be used for "pricking the skin" for "enhancement of skin permeability," in iontophoretic extraction, *see* Berner, 13:34-38, 7:11-21, and 4:7-11), and/or where the biological system may be the "***blood vessel*** tissue," would extract blood. Ex. 1003, ¶238; *see also*, U.S. Patent No. 6,501,976 ("Sohrab," Ex. 1034), 4:29-38 (describing the use of a micro-needle to extract blood).

Moreover, Berner describes an electrochemical glucose sensor in which:

> The collection reservoir may further contain an enzyme which * * * is preferably ***glucose oxidase (GOx) which catalyzes the reaction between glucose and oxygen and results in the production of hydrogen peroxide***. The hydrogen peroxide reacts at a catalytic surface of a biosensor electrode, resulting in the generation of electrons which create a detectable biosensor current (raw signal).

Berner, 13:62-14:3; *see id.*, 10:58-11:8; and 14:14-25.

Prior to the alleged invention of the '460 patent, it was also well known that glucose sensors that use a blood sample and convert blood glucose into hydrogen peroxide using oxygen (via the glucose oxidase-based enzymatic reaction), are highly sensitive to oxygen deficit. Ex. 1003, ¶¶239-240; *see also* Ex. 1026, Wang, p. 984, col. 2, ¶3 (discussing the "oxygen-deficit" problem).

As in the biosensors that Wang describes, in Berner's biosensor also "glucose oxidase (GOx)" in the collection reservoir "catalyzes the reaction

between glucose and oxygen" which "results in the production of hydrogen peroxide" used for measuring glucose, Berner, 13:62-67, and, as such, a POSITA would have known that in Berner's embodiments that use blood samples, the background or baseline signals that Berner describes (i.e., the *erroneous signals*) may include an error due to oxygen deficit. Ex. 1003, ¶241.

A POSITA would have also known that Berner's embodiments analyzing blood samples one or more membranes would be used, e.g., to limit the diffusion of glucose into the collection reservoir and to block catalase. *Id.*, ¶¶242-244; *see also*, Wang, p. 984, col. 2, ¶3 (describing the significant difference between oxygen and glucose concentrations); U.S. Patent No. 4,757,022 ("Schults," Ex. 1030) at 2:1-14 (describing the use of membrane(s) to limit glucose in addressing the oxygen-deficit problem); U.S. Patent No. 5,322,063 ("Allen," Ex. 1027), Abstract, 2:3-12, and 4:39-46 (same). A POSITA would have also known to use membrane(s) to block catalase. Ex. 1003, ¶¶245-247; *see also*, U.S. Patent No. 5,607,565 ("Azarnia," Ex. 1028) at 2:13-19 and 8:8-14 (describing the adverse effect of catalase on hydrogen peroxide in glucose sensors and the use "a cellophane membrane" to block catalase); Berner, 5:60-6:2 and 8:13-16 (describing the use of ***membranes***, that can be artificial, in ***amperometric biosensors***); Newman (Ex. 1018), p. 4594, col. 2, ¶2 (describing a cellulose acetate membrane that can block catalase); Sternberg (Ex. 1029), p. 2782, col. 1,

¶2; FIG. 1 (describing and depicting flat cellulose acetate membranes in glucose sensors such as Berner's).

A POSITA would have further understood that despite the use of a suitable semipermeable membrane, "***oxidase-based devices*** [that] rely on the use of oxygen as the physiological electron acceptor," e.g., where hydrogen peroxide is formed via a reaction between glucose and oxygen, such as in Berner's biosensor, "***are [nevertheless] subject to errors accrued from fluctuations in the oxygen tension*** and the ***stoichiometric limitation of oxygen***." *See* Wang, p. 984, col. 2, ¶ 3; Ex. 1003, ¶248.

As such, a POSITA would have known that in Berner's embodiments employing minimally invasive or invasive sampling, where the sample analyzed would include blood, the background or baseline signals that Berner describes (i.e., the *erroneous signals*) may include an error due to oxygen deficit. Ex. 1003, ¶249. Thus, Berner discloses or at least suggests this claim element. ***Id.***

As discussed above in connection with claim 14, Berner teaches or at least suggests all of the other elements of claim 56. As such, Berner renders claim 56 obvious. *Id.*, ¶250.

9. Dependent Claims 15, 21, 27, 33, 39, 45, 51, and 57

Dependent claims 15, 21, 27, 33, 39, 45, 51, and 57 each incorporates the limitations of independent claims 14, 20, 26, 32, 38, 44, 50, and 56, respectively

(all of which Berner discloses) and, additionally, each of these dependent claims recites: "*wherein the biological sample*[5] *is blood*."

In describing sampling, Berner describes:

> As used herein, the term ***"sampling" means invasive, minimally invasive or non-invasive extraction of a substance from the biological system, generally across a membrane*** such as skin or mucosa. ***The membrane can be*** . . . ***blood vessel tissue***[.] Typically, the sampling means . . . is used for extracting the analyte from the biological system into the reservoir to obtain the analyte in the reservoir. ***A "biological system" includes*** both ***living*** and artificially maintained ***systems***. ***Examples of minimally invasive and noninvasive sampling techniques include*** iontophoresis, . . . ***microfine (miniature) lances or cannulas***[.]

Berner, 5:60-6:12.

Sampling performed using "microfine (miniature) lances" where the biological system may be the "blood vessel tissue" would extract blood. Ex. 1003, ¶¶251-254. As explained above in the discussion of claim element [14.a], Berner's electrochemical biosensor performs glucose measurement and at least the

[5] This appears to be a typographical error because the respective base claims 14, 20, 26, 32, 38, 44, 50, and 56, do not recite a "biological sample." Rather, they all recite a "biological fluid." In the discussion below, this element is interpreted to mean "the biological *fluid* is blood."

collection reservoir of Berner's biosensor is in contact with the collected sample, which can be blood. Thus, Berner describes "*an electrochemical glucose sensor configured to be in contact with a blood sample to obtain a glucose measurement*." *Id.*, ¶255.

It should also be noted that in Berner's preferred embodiments, "a minimally invasive or non-invasive sampling device is used," and Berner states that "the methods of the present invention include enhancement of skin permeability by ***pricking the skin with micro-needles***." Berner, 13:34-38 and 4:7-11. A POSITA would have understood that pricking the skin with micro-needles would likely cause the sample collected from the skin to include blood. *Id.*, ¶256; *see also* Sohrab (Ex. 1034), 4:29-38.

As such, Berner teaches or at least suggests "*wherein the biological sample is blood*." Ex. 1003, ¶257.

10. Dependent Claims 16, 22, 28, 34, 40, 46, 52, and 58

Dependent claims 16, 22, 28, 34, 40, 46, 52, and 58 each incorporates the limitations of independent claims 14, 20, 26, 32, 38, 44, 50, and 56, respectively (all of which Berner discloses) and, additionally, each of these dependent claims recites: "*wherein measuring the signal response comprises measuring a current output of the electrochemical glucose sensor*." As explained above in discussing Element [14.d], Berner discloses this limitation. *See* Berner, 18:18-21 ("For the

purpose of the present sampling system, ***the electrical current measured at the sensing electrode subassembly*** is the current that is correlated with an amount of chemical signal."); *see id.*, 16:46-49; 17:15-22; and 21:60-22:2; Ex. 1003, ¶¶258-259.

11. Dependent Claims 17, 23, 29, 35, 41, 47, 53, and 59

Dependent claims 17, 23, 29, 35, 41, 47, 53, and 59 each incorporates the limitations of independent claims 14, 20, 26, 32, 38, 44, 50, and 56, respectively (all of which Berner discloses) and, additionally, each of these dependent claims recites: "*wherein measuring the signal response comprises measuring a voltage output of the electrochemical glucose sensor*." Berner taches this element in two ways, as follows:

First, Berner describes as part of screening, i.e., detecting various error conditions, detecting errors due to mechanical disturbance, where the detection is performed using "***cathodal or anodal iontophoresis voltages***." Ex. 1003, ¶¶260-262. Specifically, Berner states:

> ***If the glucose monitoring device is mechanically disturbed, there can be a larger change*** (e.g., larger relative to when the monitor is functioning under normal conditions) ***in iontophoresis voltage***. This could ***lead to an aberrant reading***. If the percentage difference between successive ***cathodal or anodal iontophoresis voltages*** is gr[e]ater than a predetermined value, for example, 15%, then an error is indicated.

Berner, 21:37-44.

Because Berner describes obtaining "***cathodal or anodal iontophoresis voltages,***" where these voltages are used to detect an error condition, by comparing a percentage difference between successive voltages with a predetermined threshold, Berner teaches "*measuring the signal response comprises measuring a voltage output of the electrochemical glucose sensor*." Ex. 1003, ¶263.

Second, Berner describes:

> In iontophoretic sampling [] there is a skin equilibration period before which measurements will generally be less accurate. ***During this equilibration period, the system voltage can be assessed and compared against an objective high voltage threshold***. If this high voltage limit is exceeded, a data screen is used to exclude the corresponding analyte measurement, since the iontophoretic current was not at a target value due to high skin resistance (as indicted by the high voltage level).

Berner, 20:36-46; Ex. 1003. ¶264. Measuring the system voltage to detect an error also constitutes "*measuring the signal response comprises measuring a voltage output of the electrochemical glucose sensor*." Ex. 1003, ¶265.

12. Dependent Claims 18, 24, 30, 36, 42, 48, 54, and 60

Dependent claims 18, 24, 30, 36, 42, 48, 54, and 60 each incorporates the limitations of independent claims 14, 20, 26, 32, 38, 44, 50, and 56, respectively (all of which Berner discloses) and, additionally, each of these dependent claims

recites: "*wherein the measured signal response is a voltage response of the electrochemical glucose sensor*." As explained above in discussing claims 17, 23, 29, 35, 41, 47, 53, and 59, Berner discloses this limitation, as well, because an output voltage measured from Berner's biosensor is also its voltage response. Ex. 1003, ¶¶266-267.

13. Dependent Claims 19, 25, 31, 37, 43, 49, 55, and 61

Dependent claims 19, 25, 31, 37, 43, 49, 55, and 61 each incorporates the limitations of independent claims 14, 20, 26, 32, 38, 44, 50, and 56 respectively (all of which Berner discloses) and, additionally, each of these dependent claims recites: "*wherein the electrochemical glucose sensor is a continuous glucose sensor*." As explained above in discussing preamble of claim 14 and Element [14.a], Berner discloses this limitation. *See* Berner, 1:14-20 (describing "methods for ***continually or continuously measuring*** the concentration of target chemical analytes" such as "for monitoring blood glucose concentrations"); s*ee id*., Abstract; Berner, 2:43-3:4 ("The transdermal sampling system is maintained in operative contact with the skin or mucosal surface of the biological system to provide for such ***continual or continuous analyte measurement***."); Ex. 1003, ¶¶268-269.

In summary, Berner teaches or at least suggests all of the elements of each of claims 14-61 and, thus, renders these claims invalid as being obvious. *Id.*, ¶270.

B. Ground 2: Claims 62-69 are obvious under 35 U.S.C. § 103 in light of Berner and Schulman.

The combination of Berner and Schulman renders independent claim 62 and each of independent claims 63-69 obvious. Ex. 1003, ¶271.

1. Independent Claim 62

Claim 62 is similar to independent claim 14, except for the following differences:

Claim 14	Claim 62
Recites a glucose sensor "in contact with a *biological fluid*,	Recites a glucose sensor "in contact with a *blood sample*."
Recites: "discard a glucose measurement, when the value associated with the severity of the erroneous signal is outside of a predetermined threshold value"	Recites: "generate a glucose value for display when the value associated with the severity of the erroneous signal satisfies a predetermined threshold value, and discard a glucose measurement when the value associated with the severity of the erroneous signal does not satisfy the predetermined threshold value"
Does not recite a "user interface"	Recites a "user interface"

As discussed below, Berner teaches a glucose sensor "in contact with a

blood sample" and the "generate" and "discard" operations recited in claim 62, and Schulman discloses the claimed "user interface." Ex. 1003, ¶¶272-273.

i. Berner discloses "an electrochemical glucose sensor configured to be in contact with a blood sample to obtain a glucose measurement"

As discussed above in connection with claim element [14.a] and dependent claim 15, Berner teaches or at least suggests "*an electrochemical glucose sensor configured to be in contact with a biological fluid to obtain a glucose measurement*" (per claim element [14.a]), "*wherein the biological [fluid] is blood.*" (per claim 15) and, thus, teaches or at least suggests this claim element. *See above*, §§ VI(A)(1)(ii) and VI(A)(9); Ex. 1003, ¶274.

ii. Berner discloses "generate a glucose value for display when the value associated with the severity of the erroneous signal satisfies a predetermined threshold value, and discard a glucose measurement when the value associated with the severity of the erroneous signal does not satisfy the predetermined threshold value"

As explained above in connection with claim element [14.h], Berner describes "*discard[ing] a glucose measurement when the value associated with the severity of the erroneous signal*" exceeds, i.e., "*does not satisfy[, a] predetermined threshold value*." Berner also discloses *generating a glucose value otherwise*, as follows:

> ***[T]he raw signals undergo a data screening method*** in order to eliminate outlier signals and/or poor (incorrect) signals using a

predefined set of selection criteria. ***In addition***, or alternatively, ***the raw signal can be converted in a conversion step***" * * * [and the] result of the conversion step is an initial signal output which provides a value which can be correlated with the concentration of the target analyte in the biological sample.

Berner, 3:23-49. Thus, the raw signals that are not eliminated during data screening would be entered into the conversion step, so that a glucose value is generated. Ex. 1003, ¶¶275-277.

Regarding discarding poor or incorrect signals having excessive error, Berner states: "***Signals that are identified as poor or incorrect in this data screen may be discarded*** or otherwise corrected for prior to any signal processing and/or conversion in order to maintain data integrity." Berner 19:37-40. This explicit disclosure of discarding poor or incorrect data mirrors the claim language for discarding results not meeting specific "screen" or threshold criteria. Ex. 1003, ¶278.

As such, Berner discloses this claim element. *Id.*, ¶279.

iii. Schulman discloses "a user interface"

Regarding a user interface, claim 62 recites:

> a user interface configured to display the generated glucose value when the value associated with the severity of the erroneous signal satisfies a predetermined threshold value,

wherein the user interface allows a user to toggle between a first screen, a second screen, and a third screen,

wherein the first screen presents the generated glucose value in a glucose measurement trend graph extending over a first time period,

wherein the second screen presents the generated glucose value in a glucose measurement trend graph extending over a second time period that is different in length from the first time period,

wherein the third screen presents the generated glucose value as a numerical value, and

wherein the user interface is configured to generate an alert responsive to detection of a hypoglycemic condition or a hypoglycemic condition based on the generated glucose value.

Berner generally discloses "an optional liquid crystal display (LCD) [that] can provide visual prompts, ***readouts*** and ***visual alarm indications***." Berner, 19:12-15. In particular, Berner describes the "setting and ***display of high and low analyte value alarms***, . . . and ***display of stored readings***." Berner, 19:18-23. International Patent Application Publication No. WO 96/00110 ("Tamada," Ex. 1021), which Berner incorporates by reference, describes that the biosensor display "may be used, for example, to allow patients to ***scroll through their present and previous analyte (e.g., glucose) level readings*** and to ***alert patients to fluctuations***

in their levels." Tamada, 30:15-18.

Based on Berner's and Tamada's description, a POSITA would have understood that scrolling through present and previous glucose readings involves displaying different screens because the present and previous glucose readings may be displayed on different screens. Ex. 1003, ¶¶280-282. Furthermore, the scrolling can include toggling between the multiple screens to the extent only one value or one set of data is shown on each screen. *Id.*, ¶282. A POSITA would have also understood that the "high and low analyte value alarms" in the context of glucose monitoring correspond to alerts of hyperglycemic and hypoglycemic conditions, respectively. *Id.*

Thus, Berner discloses, teaches, or suggests at least "a user interface configured to display the generated glucose value[s]" on different screens, to "allow a user to toggle between" multiple screens, and to "generate an alert responsive to detection of a hypoglycemic condition or a hypoglycemic condition." Berner does not explicitly describe, however, a "first screen [that] presents the generated glucose value in a glucose measurement trend graph extending over a first time period," and a "second screen [that] presents the generated glucose value in a glucose measurement trend graph extending over a second time period that is different in length from the first time period[.]" *Id.*, ¶¶283-284.

Schulman, which is directed to "[a] glucose monitoring system that continuously measures the glucose concentration in a patient's blood," *see* Schulman, 2:27-30 and Abstract, discloses all the user interface limitations of claim 62, including those that Berner does not teach explicitly. *Id.*, ¶285. In particular, Schulman discloses:

> The glucose monitor 34 displays the ***current glucose concentration*** and the ***trend*** (the rate of change over a previous period of time, e.g., fifteen minutes). The glucose concentration is presented as either a digital display of the current value, or as a graph. The concentration value is updated once each minute (or other prescribed interval). ***In the graphic display mode, the concentration is plotted at user selected intervals, showing periods of 3 to 72 hours*** … ***In the monitor mode, the glucose concentration is displayed in large numerals*** that can be easily seen from across the room, as illustrated, e.g., in FIG. 10B.

Schulman, 12:51-64. *See also* Schulman, FIG. 10B ("Current Value" mode or "monitor mode"), FIG. 10C ("Graph" mode).

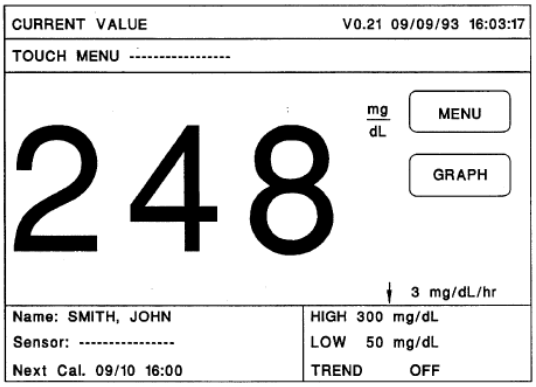

FIG. 10B

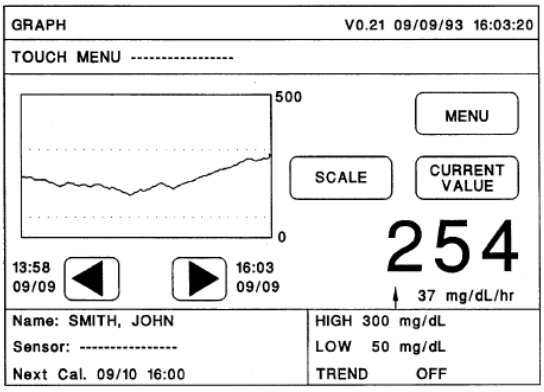

FIG. 10C

As discussed below, a POSITA would have understood that Schulman discloses all three types of user interface "screens" and the related toggling that claim 62 recites. Ex. 1003, ¶286.

First, in the "graphic display mode," Schulman teaches that a user could select different time periods ranging from 3 to 72 hours to plot "***trend*** (the rate of change over a previous [user-selected] period of time . . .)" of glucose concentration. Schulman, 12:51-64. Thus, if the user chose a 3-hour period for the graphic display, then the glucose monitor would display a first screen presenting "the generated glucose value in a glucose measurement trend graph extending over a first time period [of 3 hours]"; if the user chose a 72-hour period for the graphic display, then the glucose monitor would display a second screen presenting "the generated glucose value in a glucose measurement trend graph extending over a second time period [of 72 hours], wherein the "second time period [] is different in length from the first time period." Ex. 1003, ¶287.

Second, in the "monitor mode," Schulman teaches that a different screen displays the glucose concentration is "in large numerals[.]" In other words, the monitor mode displays a third screen presenting "the generated glucose value as a numerical value." Schulman, 12:51-64; FIGS. 10B and 10C; Ex. 1003, ¶288.

Third, Schulman discloses that various menu buttons can be selected by the user to switch between the display modes and screens:

> FIG. 10A, for example, shows the main menu screen displayed by the glucose monitor when in use. ***FIG. 10B depicts the current value screen displayed by the monitor when the current value selection is made from the main menu.*** Note the large size of the glucose measurement displayed, providing easy-to-read numbers that are several inches high. ***FIG. 10C depicts a representative graph of the glucose concentration that is generated and displayed by the glucose monitor when the graphic selection is made from the main menu.***

Schulman, 14:42-51. The ability to switch display modes, coupled with the above-described ability to select time periods of different length to plot trend graphs, "allow[s] a user to toggle between the first screen, the second screen, and the third screen." Ex. 1003, ¶¶289-290.

In addition, Schulman also teaches "generat[ing] an alert responsive to detection of a hyperglycemic condition or a hypoglycemic condition." *See* Schulman, 2:29-32 ("The system further automatically determines whether the

measured concentration and rate of change are within certain preset limits, and if not, generates an alarm signal."); 13:17-21 ("an alarm that signals when the value of the most recent reading is below or above user-set (or, if none, default) low or high limits"). *Id.*, ¶291.

Thus, Schulman discloses all the "user interface" limitations of claim 62. *Id.*, ¶292.

Berner teaches some of the claimed user interface features, as discussed above, and all of the other elements of claim 62, as discussed above and in connection with claim 14. Therefore, the combination of Berner and Schulman teaches or suggests all the elements of claim 62. *Id.*, ¶294.

2. A POSITA Would Have Been Motivated to Combine Berner and Schulman.

A POSITA would have been motivated to combine Schulman's teachings with Berners's glucose sensor to improve its user interface capabilities, which can be important in the continuous monitoring system that Berner describes. Ex. 1003, ¶295. As a threshold matter, both Berner and Schulman are directed to glucose monitoring/display systems having electrochemical glucose sensors.

A POSITA would have readily understood that Schulman's display can improve Berner's glucose sensor because Schulman describes the advantage of detecting "trends" and accordingly teaches that "[s]uch stored data may also advantageously be viewed, as selected, as a graphic display that indicates the last

several hours of recorded values, ***thereby clearly showing any trends in the data over such time period***.”). Schulman, 2:57-61; Ex. 1003, ¶296.

In addition, a POSITA would have been capable of modifying Berner’s display to incorporate Schulman’s graphical display functions because only a few well-understood modifications would be required, such as reprogramming Berner’s microprocessor and reconfiguring or substituting Berner’s display unit with Schulman’s enhanced graphical display showing glucose graphs over user-selectable time periods. At the time of the claimed invention (i.e., in 2003), no significant technological obstacle would have prevented a POSITA from making such modification. Ex. 1003, ¶297.

After all, the user interface and its functions are substantially independent of the electrochemical glucose cell and analysis of the sensed signals. As such, a POSITA would have considered the display unit and the software program in Berner’s sensor to be modular components that could be easily adapted from or replaced with another display/user interface and software, respectively, from a similar glucose sensor system such as Schulman’s. *Id.*, ¶298.

Thus, modifying Berner’s display according to Schulman’s teachings would require little more than: (a) combining one known element in the prior art (*i.e.*, Schulman’s display functions) with other known elements (*i.e.*, Berner’s display), or (b) simply substituting one known element (*i.e.*, the display of Berner’s

biosensor system) with another known element (*i.e.*, Schulman's user interface module). *Id.*, ¶299.

A POSITA would also have expected the modification to succeed. Because Berner and Schulman both describe electrochemical sensors for continuous monitoring of glucose in the body, and because the improvements to the display functionality that Schulman describes can be implemented readily by modifying the software and/or the display module, and do not require any modifications to the transdermal fluid extraction apparatus and the electrochemical cell of Berner, a POSITA would therefore have had strong expectations of successfully combining the teachings of these two references. *Id.*, ¶300.

In summary, because the straightforward modifications to Berner's glucose sensor according to Schulman's teachings would have been well within the grasp of a POSITA, it would have been obvious to combine the teachings of Berner and Schulman to make an improved sensor, i.e., the claimed invention. *Id.*, ¶¶301-302.

3. Independent Claims 63-69

Each of these claims is substantially the same as independent claim 62, but the claim element "wherein the erroneous signal is associated with at least one condition selected from [a *Markush* group]" of claim 62 is replaced as shown in the table below.

Claim	Element "wherein the erroneous signal is associated with at least one condition selected from [a *Markush* group]" of claim 62 is replaced with:	Replaced element is also recited in claim
63	"wherein the erroneous signal is associated with an available electrode surface area"	20
64	"wherein the erroneous signal is associated with a temperature associated with the electrochemical glucose sensor"	26
65	"wherein the erroneous signal is associated with a local environment associated with the electrode surface of the first electrode"	32
66	"wherein the erroneous signal is associated with a diffusion transport of glucose or a measured species"	38
67	"wherein the erroneous signal is associated with a pressure or a stress associated with the electrochemical glucose sensor"	44
68	"wherein the erroneous signal is associated with a biochemical species"	50
69	"wherein the erroneous signal is associated with an oxygen deficit"	56

Ex. 1003, ¶303.

It is discussed above that the combination of Berner and Schulman teaches all of the elements of claim 62. Moreover, it is also explained above in the discussion of claims 20, 26, 32, 38, 44, 50, and 56, that Berner teaches the

respective elements of claims 63-69 that are identified in the table above. *See above*, §§ VI(A)(1)-(8). Therefore, Berner in view of Schulman teaches all of the elements of claims 63-69. Ex. 1003, ¶304.

Since it would have been obvious for a POSITA to combine Berner and Schulman, which collectively teach each and every element of independent claims 62 and of independent claims 63-69, as well (as shown above), Berner in view of Schulman renders claims 62-69 obvious. *Id.*

VII. CONCLUSION

In light of the above, it is respectfully submitted that claims 14-69 of the '460 Patent are unpatentable under 35 U.S.C. § 103. Petitioner respectfully requests that an *inter partes* review be instituted and the subject claims be cancelled.

VIII. MANDATORY NOTICES

A. Real Parties-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Petitioner identifies AgaMatrix, Inc. as the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

As of the filing date of this petition, the '460 Patent is involved in litigation in the District of Delaware in *Dexcom, Inc. v. AgaMatrix, Inc.*, Case No. 1:17-cv-01310; and before United States International Trade Commission, in *Certain*

Electrochemical Glucose Monitoring Systems And Components Thereof, Investigation No. 337-TA-1075.

Concurrently with this petition, Petitioner is also filing: (a) an IPR petition (2018-01718) to challenge the patentability of claims 14-18, 20-24, 26-30, 32-36, 38-42, 50-54, 62-66, and 68 of the '460 patent on different, but equally compelling, grounds; and (b) IPR petitions (IPR2018-01715 and IPR2018-01716) to challenge the patentability of certain claims of U.S. Patent No. 9,724,045 which is commonly owned, and shares the same specification and parents, as the '460 Patent.

Petitioner is not aware of any other judicial or administrative matter that would affect or be affected by a decision in this IPR.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3) and Service Information Under 37. C.F.R. § 42.8(b)(4)

Lead Counsel	***Back-up Counsel***
Ira J. Levy (Reg. No. 35,587) ILevy@goodwinlaw.com GOODWIN PROCTER LLP 620 8th Avenue New York, NY 10018 (212) 813-8800	Suhrid Wadekar (Reg. No. 65,595) SWadekar@goodwinlaw.com GOODWIN PROCTER LLP 100 Northern Avenue Boston, MA 02210 (617) 570-1000

Pursuant to 37 C.F.R. § 42.8(b)(4), counsel agrees to service by mail as detailed above, and to electronic service by email to the email addresses above. A

Power of Attorney executed by Petitioner accompanies this Petition.

Fees: The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 506989.

D. Service on the Patent Owner

Pursuant to 37 C.F.R. § 42.105(a), this petition and its exhibits were served simultaneously with this filing on Patent Owner at the correspondence address of record on file at the USPTO for the '460 Patent, per the attached Certificate of Service, with a copy to Patent Owner's counsel in the above-referenced litigation matters.

IX. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.104, Petitioner certifies that this Petition is being filed within one year of AgaMatrix, Inc. being served with a complaint for infringement. Petitioner has not filed a civil action challenging the '460 Patent, the patent is available for *inter partes* review, and that Petitioner is not barred from requesting *inter partes* review of the '460 Patent.[6]

[6] The Complaint alleging infringement of the '460 Patent in *Dexcom, Inc. v. AgaMatrix, Inc.*, Case No. 1:17-cv-01310 (D. Del.) was served on Sept. 15, 2017.

Date: September 14, 2018

Respectfully submitted,

By */s/ Ira J. Levy*

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,750,460** complies with the type-volume limitation of 37 C.F.R. §§42.24(a)(1)(i) and 42.24(b)(1). The Petition contains 13,805 words, excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1), as measured by the word-processing system use to prepare the Petition.

Certificate of Service

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that on September 14, 2018, I caused a true and correct copy of the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,750,460** and copies of all supporting materials to be served by Federal Express Next Business Day Delivery on the patent owner at the correspondence address of record for the subject patent as listed on PAIR:

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